UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,573	11/02/2005	Lawrence Carl Panasci	ON/4-32760A	4455

1095 7590 04/20/2009

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
04/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,573	PANASCI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-13* is/are pending in the application.

4a) Of the above claim(s) *8,9,12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 1/29/2009, are acknowledged and entered. Claims 1-4 and 6-13 are pending and under examination. Claims 8-9 and 12-13 remain withdrawn from consideration.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites a combination comprising chlorambucil and imatinib wherein chlorambucil and imatinib are present in "synergistically effective amounts". The metes and bounds of this claim limitation are not clear. For example, imatinib is disclosed in the specification to be administered at a dose ranging from 50 to 1000 mg and chlorambucil to be administered at a dose of 0.2 to 1 mg/kg/day. However, Applicants provide no guidance with respect to what amounts of imatinib and chlorambucil in a "combination" are "synergistically effective" amounts. Further, claim 3 is also unclear with respect to what the "synergistically effective" amounts are synergistically effective *for*.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicant directs the Examiner's attention to the last paragraph on page 12 of the specification which is purported to describe appropriate concentrations of imatinib for synergy and indicates that the synergy "does not appear to be dose dependent". Based on this information, Applicant argues that one of ordinary skill in the art would have no difficulty determining the metes and bounds of claim 3.

In response, the Examiner respectfully submits that the fact that sensitization using 5 and 10 mM Compound I (imatinib) in vitro in combination with chlorambucil does not adequately define the metes and bounds of "synergistically effective amounts" as recited in claim 3. Claim 3

depends from claim 1, which is drawn to combinations of imatinib and a nitrogen mustard analogue, not methods of treatment. Claim 1 comprises any amount of imatinib and said nitrogen mustard analogue. Claim 3, being dependent from claim 1, further limits the combination of claim 1 to only combination wherein imatinib and nitrogen mustard analogue are present in synergistically effective amounts. Whereas the specification discloses amounts of imatinib and nitrogen mustard analogues to be administered, the specification does not disclose what amounts of imatinib and nitrogen mustard analogues are generally synergistic. As such, one skilled in the art would not know what amounts of imatinib and nitrogen mustard analogue in combination are synergistically effective as recited in claim 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-7, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by **Virchis *et al.*** (Blood, 2000, vol. 96(11), Part 1, p. 82A) (reference AR on IDS filed May 11, 2005).

Virchis *et al.* teach a combination of chlorambucil and STI-571 (*i.e.*, imantinib) that is applied to CLL cells obtained from 9 CLL patients. Chlorambucil is administered to cells at a fixed concentration of 25 μg/mL (82 μM) and STI-571 at a concentration of 10 μM. The reference thus anticipates the claimed combinations for "simultaneous, separate, or sequential use" comprising chlorambucil and imatinib.

With regard to claims 5 and 6 which recite that the combination is "used for" the treatment of CLL or "used in" a preparation of a medicament for the treatment of CLL, these limitations are not given patentable weight because they do not result in a material difference between the claimed combination and that taught in Virchis *et al.*, which is clearly capable of being used for the treatment of CLL or used in a preparation of a medicament for the treatment of CLL.

Applicant's arguments have been carefully considered but they are not deemed persuasive. Applicant argues that Virchis et al. teach away from the claimed combination. This is not persuasive because even it were accepted that Virchis et al. "teach away" from the claimed combinations, such is an argument traversing a 35 U.S.C. 103 rejection, not a 35 U.S.C. 102 rejection as is the case here. Virchis et al. teach a combination of imatinib and chlorambucil for the treatment of CLL. As such, Virchis et al. anticipate the claimed combinations as recited in claims 1-7 and 10. The intended use of the claimed combination (i.e., "for the treatment of patients with chronic lymphocytic leukemia") does not result in a patentable distinction over the cited prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-7, and 10 are again rejected under 35 U.S.C. 103(a) as being unpatentable over **Kimby *et al.*** (Acta Oncol., 2001, vol. 40, nos. 2-3, pages 224-230) and **Tallman** (Semin. Hematol., 2002, vol. 39, no. 4, suppl. 3, pages 1-5) in view of **Esteve *et al.*** (Haematologica, 1997, vol. 82, pages 596-599).

Kimby *et al.* teach that the primary treatment of patients with symptomatic B-CLL is the oral alkylating agent, chlorambucil (Abstract). The reference does not teach imatinib.

Tallman teaches that imatinib mesylate has "remarkable activity" in patients with chronic myeloid leukemia (CML) (Abstract). The reference does not teach chlorambucil.

Esteve *et al*. teach that occasionally, CML and CLL coexist in the same patient with most cases corresponding to patients who develop CML during the evolutive course of CLL (page 596, left column). In other cases, both disorders are diagnosed simultaneously (*id*.).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising chlorambucil and imatinib for simultaneous, separate, or sequential use in the treatment of leukemia. The motivation to do so would be to develop a drug combination that could be predictably used to treat patients simultaneously diagnosed with CLL and CML. The skilled artisan would have been imbued with at least a reasonable expectation that such a combination, comprising drugs known to be clinically effective for the treatment of CLL (chlorambucil) and CML (imatinib), would be also be effective for the treatment of these leukemias in patients who are diagnosed with both leukemia types simultaneously as taught in Esteve *et al*.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that Virchis et al. teach away from the present combination based on the fact that Virchis et al. activation of c-Abl protein tyrosine kinase couples DNA damage induction by chlorambucil to p53 upregulation and subsequent apoptosis in B-CLL cell lines. Because imatinib is a specific inhibitor of c-Abl kinase, Applicants assert that it counteracts the effect of chlorambucil. However, chlorambucil and imatinib were both known in the art to be useful in the treatment of B-CLL (chlorambucil) and CML (imatinib) and it was further known in the art that B-CLL and CML occasionally coexist in the same patients. As such, it would have been prima facie obvious to formulate a combination of chlorambucil and imatinib for the treatment of such patients. Applicant's results of synergism in vitro in a particular leukemia cell line are not evidentiary of an unexpected result of the claimed combination in comparison to the cited prior art. In other words, Applicants have presented no evidence of unexpected results in treating a patient having both B-CLL and CML as suggested and motivated by the cited prior art.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Kimby *et al.*** and **Tallman** in view of **Esteve *et al.*** as applied to claims 1-4, 6-7, and 10 above, and further in view of **MacLeod *et al.*** (USP No. 5,506,257; Issued Apr. 9, 1996).

Kimby *et al.*, Tallman, and Esteve *et al.* teach as discussed *supra* and the same teachings are applied herein in their entirety. Claim 11 differs from Kimby *et al.*, Tallman, and Esteve *et al.* in that Kimby *et al.*, Tallman, and Esteve *et al.* do not disclose a commercial package.

However, it would have been *prima facie* obvious to provide the combination of chlorambucil and imatinib in a commercial package with instructions so as to provide ease of distribution of the combination to physicians and patients with instructions on dosing and potential side effects. Such commercial packages are well known in the art. For example, MacLeod *et al.* teach that pharmaceuticals can be provided in a commercial kit containing the active agent(s) and instructions for treatment of a disorder (col. 7, lines 51-66).

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that the rejection should be withdrawn based upon Applicant's arguments pertaining to the rejection of claims 1-4, 6-7, and 10, supra. For the reasons discussed supra, such rejection is maintained.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Virchis *et al.*** as applied to claims 1-4, 6-7, and 10 above, and further in view of **MacLeod *et al.*** (USP No. 5,506,257; Issued Apr. 9, 1996).

Virchis *et al.* teach as discussed *supra* and the same teachings are applied herein in their entirety. Claim 11 differs from Virchis *et al.* in that Virchis *et al.* do not disclose a commercial package.

However, it would have been *prima facie* obvious to provide the combination of chlorambucil and imatinib in a commercial package with instructions so as to provide ease of distribution of the combination to physicians and patients with instructions on dosing and potential side effects. Such commercial packages are well known in the art. For example, MacLeod *et al.* teach that pharmaceuticals can be provided in a commercial kit containing the active agent(s) and instructions for treatment of a disorder (col. 7, lines 51-66).

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that the rejection should be withdrawn based upon Applicant's arguments pertaining to the rejection of claims 1-4, 6-7, and 10, supra. For the reasons discussed supra, such rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614